Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort

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Summary

Background **The monoclonal antibody trastuzumab has survival benefit when given with chemotherapy to patients with early, operable, and metastatic breast cancer that has HER2 (also known as ERBB2) overexpression or amplification. We aimed to assess event-free survival in patients with HER2-positive locally advanced or inflammatory breast cancer receiving neoadjuvant chemotherapy with or without 1 year of trastuzumab.**

Methods **We compared 1 year of treatment with trastuzumab (given as neoadjuvant and adjuvant treatment; n=117) with no trastuzumab (118), in women with HER2-positive locally advanced or inflammatory breast cancer treated with a neoadjuvant chemotherapy regimen consisting of doxorubicin, paclitaxel, cyclophosphamide, methotrexate, and fluorouracil. Randomisation was done with a computer program and minimisation technique, taking account of geographical area, disease stage, and hormone receptor status. Investigators were informed of treatment allocation. A parallel cohort of 99 patients with HER2-negative disease was included and treated with the same chemotherapy regimen. Primary endpoint was event-free survival. Analysis was by intention to treat. This study is registered, number ISRCTN86043495.**

Findings **Trastuzumab significantly improved event-free survival in patients with HER2-positive breast cancer (3-year event-free survival, 71% [95% CI 61–78; n=36 events] with trastuzumab, *vs* 56% [46–65; n=51 events] without; hazard ratio 0·59 [95% CI 0·38–0·90]; p=0·013). Trastuzumab was well tolerated and, despite concurrent administration with doxorubicin, only two patients (2%) developed symptomatic cardiac failure. Both responded to cardiac drugs.**

Interpretation **The addition of neoadjuvant and adjuvant trastuzumab to neoadjuvant chemotherapy should be considered for women with HER2-positive locally advanced or inflammatory breast cancer to improve event-free survival, survival, and clinical and pathological tumour responses.**

Funding **F Hoffmann-La Roche.**

Introduction

Locally advanced breast cancer accounts for 6–10% of new cases of breast cancer and has a worse prognosis than does early operable disease, although patients with locally advanced disease have a better outlook than do those with distant metastases.[1,2] Inflammatory breast cancer is a rare clinical and pathological subtype that follows an aggressive course and needs systemic therapy even when apparently localised. Preoperative systemic (neoadjuvant) therapy has an important role in patients with locally advanced and inflammatory cancers, treating distant micrometastases, downstaging tumours, improving operability, and sometimes allowing breast-conserving surgery to take place.[3] Anthracycline-based and taxane-based therapies are frequently used as preoperative treatments. In patients with operable disease, a non-cross-resistant regimen containing both agents was well tolerated and produced high response rates (78%) and rates of breast-conserving surgery (63%), with a low frequency of symptomatic cardiac dysfunction (≤0·5%).[4]

Amplification or overexpression, or both, of human epidermal growth factor receptor-2 (HER2, also known as ERBB2), a transmembrane receptor tyrosine kinase, is present in around 22% of early breast cancers, 35% of locally advanced and metastatic tumours, and 40% of inflammatory breast cancers, and is associated with aggressive disease and poor prognosis.[5,6] Patients with HER2-positive locally advanced or inflammatory breast cancer are therefore in particular need of effective treatment. Trastuzumab (Herceptin, Roche, Basel, Switzerland), a recombinant humanised monoclonal antibody that targets HER2, has efficacy as monotherapy[7,8] and improves results of chemotherapy in patients with HER2-positive metastatic[9,10] and early

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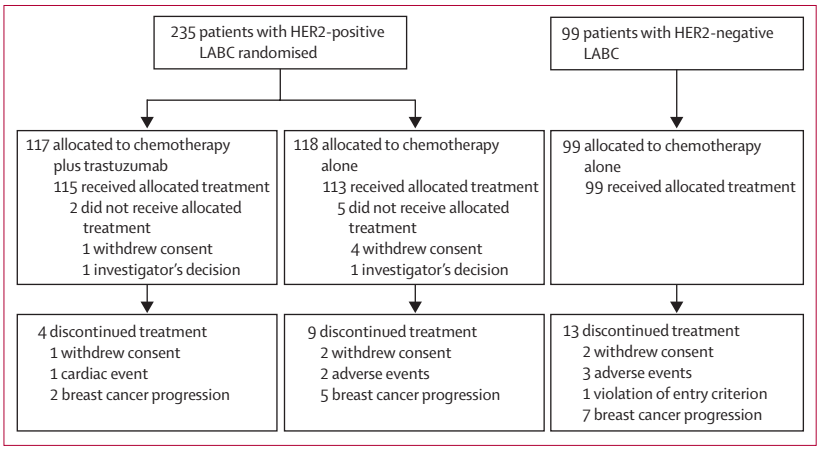


Figure 1: **Trial profile**
We did not record the total number of patients assessed for eligibility. LABC=locally advanced breast cancer.

	HER2-positive disease		HER2-negative disease
	With trastuzumab (n=117)	Without trastuzumab (n=118)	Without trastuzumab (n=99)
Stage group			
T4 non-inflammatory	49 (42%)	51 (43%)	44 (44%)
Inflammatory	32 (27%)	31 (26%)	14 (14%)
N2 or ipsilateral nodes	36 (31%)	36 (31%)	41 (41%)
Hormone-receptor status			
OR or PR positive, or both	42 (36%)	42 (36%)	63 (64%)
Both negative	75 (64%)	76 (64%)	36 (36%)
Age			
<50 years	50 (43%)	50 (42%)	48 (48%)
>50 years	67 (57%)	68 (58%)	51 (52%)
Axillary nodes			
N0	16 (14%)	19 (16%)	17 (17%)
N1	50 (43%)	53 (45%)	38 (38%)
N2	50 (43%)	46 (39%)	44 (44%)
Unknown	1 (1%)	0	0
Ipsilateral supraclavicular nodes			
No	110 (94%)	111 (94%)	95 (96%)
Yes	7 (6%)	5 (4%)	4 (4%)
Unknown	0	2 (2%)	0
Baseline LVEF	63% (55–82)	63% (55–89)	63% (56–79)

Data are n (%) or median (IQR). OR=oestrogen receptor. PR=progesterone receptor. LVEF=left ventricular ejection fraction.

Table 1: **Baseline characteristics**

operable breast cancer.[11–13] It is widely approved for use as monotherapy and in combination with chemotherapy or hormone therapy in these patients, but not specifically in those with locally advanced or inflammatory breast cancer. In a pilot study,[14] anthracycline and paclitaxel were successfully combined with trastuzumab in patients with metastatic disease. To reduce risk of cardiac toxic effects, only three cycles of doxorubicin were given in the pilot study, which corresponds to a cumulative dose of 180 mg per m² of body surface area.[15] No patient developed symptomatic cardiac dysfunction, although four patients (of 16) had reversible asymptomatic decreases in left ventricular ejection fraction to 50% or lower.

The neoadjuvant Herceptin (NOAH) study was designed to assess efficacy of neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone in patients with HER2-positive locally advanced or inflammatory breast cancer.

Methods

Study design

NOAH was an international, open-label, phase 3 trial in women with newly diagnosed locally advanced or inflammatory breast cancer. We randomly allocated patients with HER2-positive disease to receive neoadjuvant trastuzumab plus chemotherapy followed by adjuvant trastuzumab, or neoadjuvant chemotherapy alone. However, after positive results of adjuvant trastuzumab trials became available, HER2-positive patients allocated to chemotherapy alone were offered 1 year of adjuvant trastuzumab postsurgery. Because prospective data comparing treatment outcomes of HER2-positive patients with those of patients with HER2-negative disease were scarce, a parallel observational cohort was prospectively included, in which women with HER2-negative disease were selected with the same criteria as were those with HER2-positive disease, and received the same chemotherapy as did the HER2-positive group, but without trastuzumab.

Our primary objective was to compare event-free survival, which was defined as time from randomisation to disease recurrence or progression (local, regional, distant, or contralateral) or death from any cause, in patients with HER2-positive disease treated with and without trastuzumab. Secondary endpoints were pathological complete response in breast tissue, total pathological complete response (in breast and axilla), overall clinical response rates, cardiac safety, and survival in all three groups of patients, and event-free survival (measured from study registration) in patients with HER2-negative disease. The study was done in 27 centres and six countries by the Michelangelo and Solid Tumor Intensification (SOLTI) groups and independent centres. The study protocol was approved by institutional review boards and all patients gave written informed consent.

Randomisation and masking

Randomisation was done centrally at the Michelangelo operations office with a computer program and a minimisation technique,[16] taking account of geographical area, disease stage, and hormone status. Patients with HER2-negative tumours were stratified according to the same prespecified variables and randomly allocated to the parallel study cohort or not, with the same minimisation technique and a ratio of 1 (study) to 3 (off-study). This ratio

was used to ensure that patients with HER2-negative tumours, which are roughly three times more common than are HER2-positive tumours, were enrolled and treated during the same timeframe as were their HER2-positive counterparts. Patients not allocated to the parallel cohort were treated outside the trial according to the investigators' routine practice. Investigators were informed of treatment allocation by fax from the Michelangelo operations office.

Patients

To be eligible, patients had to have histologically proven locally advanced breast cancer, defined as T3N1 or T4 (skin or nipple invasion, peau d'orange, extension into chest wall or inflammatory carcinoma), or any T plus N2 or N3, or any T plus involvement of ipsilateral supraclavicular nodes. Patients entering the randomised part of the study had HER2-positive disease, which was defined as 3+ overexpression by immunohistochemical testing (Herceptest, Dako, Glostrup, Denmark) or HER2 amplification by fluorescent in-situ hybridisation (Pathvysion HER2 test, Abbott/Vysis, Des Plaines, IL, USA) according to a central laboratory (Klinikum Kassell, Kassell, Germany). Patients in the parallel observational group had HER2-negative tumours, which were defined as 0 or 1+ overexpression on the basis of local laboratory testing. All patients had to have tumour hormone receptors assessed and to have at least one measurable lesion according to response evaluation criteria in solid tumours[17] (with a minimum indicator lesion size of 20 mm when measured by palpation) or inflammatory carcinoma.

Patients had to be adult women with adequate hepatic, renal, and bone marrow function, an Eastern Cooperative Oncology Group performance status 1 or lower, and a left ventricular ejection fraction of 55% or higher measured by multiple gated acquisition scan or echocardiography. Women of childbearing potential had to use contraception. Several exclusion criteria applied: bilateral breast cancer; metastases (other than in ipsilateral supraclavicular nodes); previous treatment for invasive malignant disease; previous or concurrent malignant disease other than basal-cell carcinoma of the skin or in-situ cervical cancer; pregnancy or lactation; use of other investigational drugs within the past 30 days; and other serious illness or medical disorders including cardiac failure, New York Heart Association (NYHA) class II or higher.

Procedures

All patients received the same intravenous neoadjuvant chemotherapy regimen, consisting of several non-cross-resistant cytotoxic agents: doxorubicin 60 mg/m² (given first) plus paclitaxel 150 mg/m² infused during 3 h, every 3 weeks for three cycles, followed by paclitaxel 175 mg/m² administered every 3 weeks for four cycles. Cyclophosphamide (600 mg/m²), methotrexate (40 mg/m²), and fluorouracil (600 mg/m²) were then given on days 1 and 8 every 4 weeks for three cycles. Surgery followed by radiotherapy was scheduled after completion of chemotherapy in all patients. Patients with oestrogen or progesterone receptor-positive disease received adjuvant tamoxifen 20 mg per day for 5 years.

Participants allocated to receive trastuzumab received a loading dose of 8 mg per kg of bodyweight infused intravenously during 90 min, followed by ten cycles of 6 mg/kg during 30 min every 3 weeks alongside chemotherapy. Trastuzumab could be given every 4 weeks during cyclophosphamide, methotrexate, and fluorouracil chemotherapy. After surgery, additional cycles of trastuzumab were given, starting before or during radiotherapy (at the investigator's discretion), to complete 1 year of trastuzumab treatment.

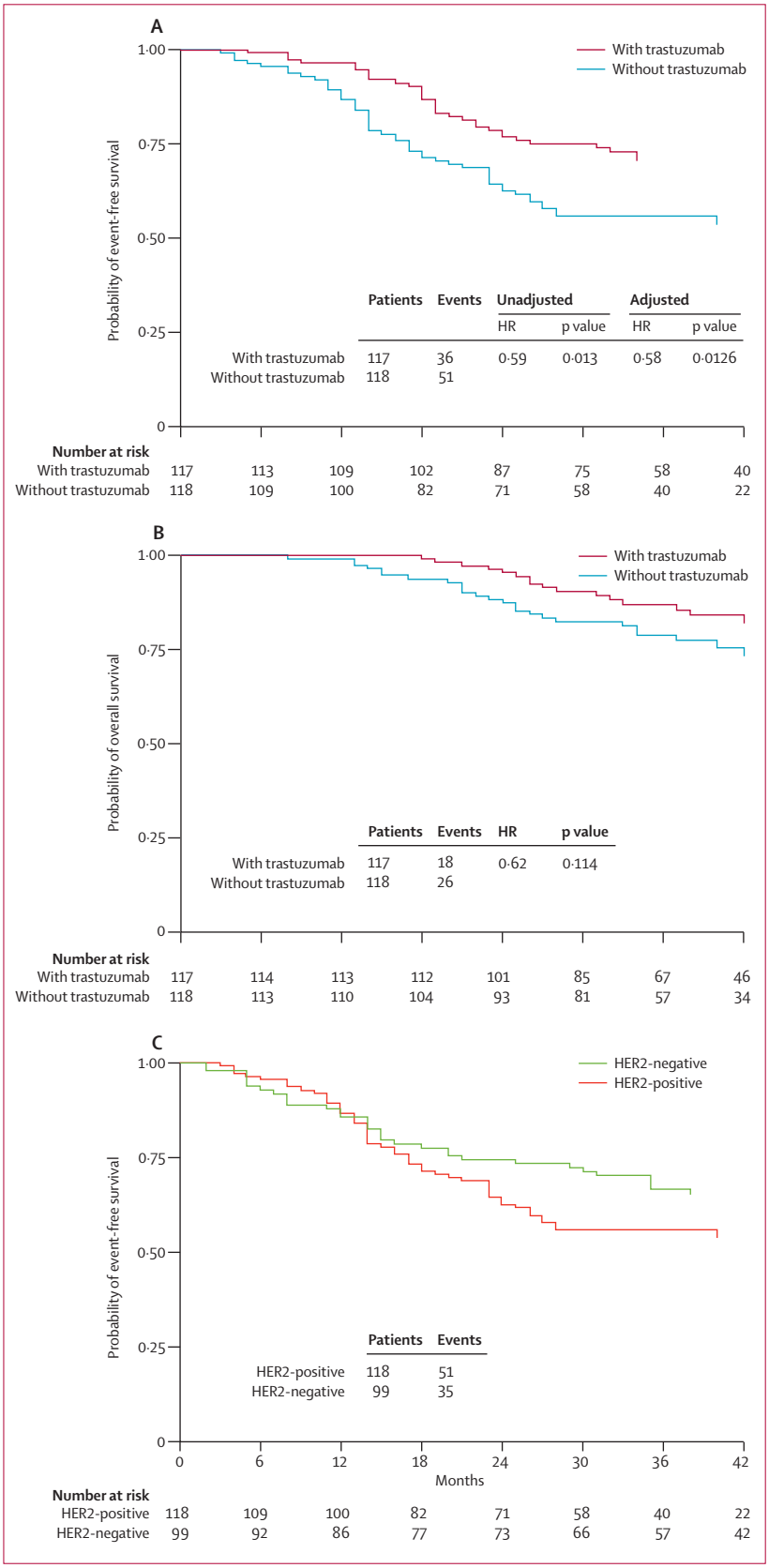
We scheduled chemotherapy dose reductions and delays for clinically significant grade 3 or 4 haematological and non-haematological toxic effects according to protocol-defined criteria. Trastuzumab was temporarily withheld until recovery for related reversible non-haematological grade 3 or 4 toxic effects (other than cardiac), and was discontinued for congestive heart failure or a fall in left ventricular ejection fraction to lower than 45% when confirmed by a second measurement 3 weeks later. Patients with falls in left ventricular ejection fraction to 45–49% could continue trastuzumab if the absolute drop was lower than 10% or was transient.

We assessed tumour response by clinical examination, mammogram, or ultrasound at baseline and before surgery, and by pathological examination of surgical specimens after primary systemic therapy. Subsequently, patients were checked for possible disease recurrence 2 months after completion of radiotherapy, then every 6 months until 5 years after surgery, then yearly until 10 years after surgery, with yearly chest radiographs and mammograms throughout. Reports of local and regional recurrence and invasive contralateral breast cancer needed cytological or histological evidence; bone and visceral recurrences were diagnosed on the basis of radiological evidence.

Adverse events were assessed clinically and by haematological and biochemical measurements throughout chemotherapy. Adverse events (including cardiac) were graded according to National Cancer Institute common toxicity criteria version 2.0.[18] Cardiac function was assessed clinically by electrocardiogram and echocardiography or multiple gated acquisition scan at baseline, completion of doxorubicin plus paclitaxel, completion of paclitaxel, before surgery, and end of trastuzumab treatment or 1 year from first dose of chemotherapy. Cardiac safety was monitored by independent cardiologists within a cardiac advisory board.

Statistical analysis

Enrolment of 116 patients was planned for the HER2-positive treatment groups to provide 86 primary outcome



events. Assuming 50% rate of event-free survival at 3 years with chemotherapy alone, and a median event-free survival of 5·5 years with trastuzumab (corresponding to a 68·5% rate at 3 years), a log-rank test needed 86 events to achieve 80% power to detect a hazard ratio (HR) of 0·545 (absolute improvement of 18·5% in event-free survival rate) at a two-sided significance level of 5%. Sample-size calculations were based on the work of Collett[19] and the software Nquery 5.0. A sample size of 100 was chosen pragmatically for the HER2-negative group to roughly match sample size in the HER2-positive groups, leading to a total planned recruitment of 332 patients.

All randomly assigned patients were included in efficacy analyses, which were by intention to treat. χ^2 tests for categorical data and log-rank tests for time-to-event endpoints provided two-sided p values. We calculated Kaplan-Meier curves and used these to estimate 3-year event-free survival rates and 95% CIs. Cox proportional-hazards regression analysis was used to estimate HRs and 95% CIs. We also planned exploratory analysis of event-free survival in key subsets of patients (according to presence or absence of inflammatory disease, hormone receptor status, clinical nodal status, and achievement or not of pathological complete response in breast tissue).

Analyses of clinical and pathological response rates were scheduled before final analysis, when all patients had completed surgery, and these results were presented.[20–23] Safety data were monitored throughout the study and a formal interim safety analysis was done when the first 50 HER2-positive patients completed treatment. Final analysis was done after 87 events were reported. All statistical analyses were done with the software SAS (version 9.0).

This study is registered, number ISRCTN86043495 (Roche study number MO16432).

Role of the funding source

The sponsor did not have a role in data analysis, but had a role in writing of the report. The Michelangelo group was responsible for data gathering and analysis. The corresponding author had responsibility for the decision to submit for publication.

Results

Between June 20, 2002, and Dec 12, 2005, 334 patients entered the study. Figure 1 shows the trial profile. One patient with HER-positive disease who was allocated to receive trastuzumab was not included in event-free and overall survival analyses because of delayed approval of a protocol amendment by the ethics committee at that site.

Figure 2: **Event-free and overall survival**
(A) Event-free survival in the HER2-positive (intention-to-treat) population. (B) Overall survival in the HER2-positive (intention-to-treat) population. (C) Event-free survival in HER2-positive (without trastuzumab) and HER2-negative (intention-to-treat) populations (HR and p value not calculated because patients were not randomly assigned). Hazard ratios were obtained from the unadjusted Cox model unless stated otherwise. HR=hazard ratio.

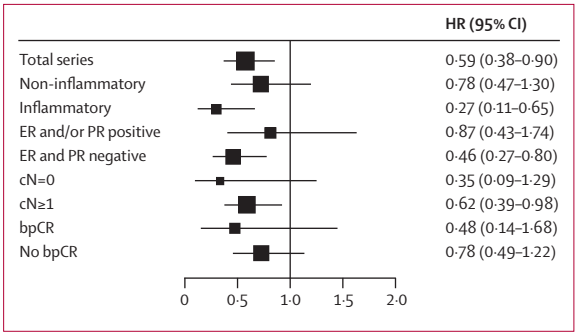


Figure 3: **Analyses of event-free survival by subgroup in patients with HER2-positive disease**

Hazard ratios (with 95% CIs) obtained from unadjusted Cox model are shown for patients assigned to trastuzumab compared with those assigned to no trastuzumab. Solid vertical line shows a hazard ratio of 1·0, which is the null-hypothesis value (no difference between patients treated with or without trastuzumab). Size of the squares is proportional to number of events in the subgroup, and length of the horizontal lines shows CI. ER=oestrogen receptor. PR=progesterone receptor. cN=clinical nodal stage. bpCR=pathological complete response in breast tissue.

	HER2-positive disease		p value*	HER2-negative disease	p value†
	With trastuzumab (n=117)	Without trastuzumab (n=118)		Without trastuzumab (n=99)	
bpCR	50 (43%)	26 (22%)	0·0007	17 (17%)	0·37
tpCR	45 (38%)	23 (19%)	0·001	16 (16%)	0·52
OR‡	102 (87%)	87 (74%)	0·009	70 (71%)	0·62

Data are n (%). bpCR=pathological complete response in breast tissue. tpCR=total pathological complete response (in breast and axillary nodes). OR=overall response. *For comparison of HER2-positive disease groups. †For comparison of without trastuzumab groups. ‡Complete and partial clinical responses.

Table 2: **Pathological responses to treatment**

	HER2-positive disease		HER2-negative disease
	With trastuzumab (n=115)	Without trastuzumab (n=113)	Without trastuzumab (n=99)
Adverse events (all grades, irrespective of causality)			
All	113 (98%)	113 (100%)	97 (98%)
Cardiac events	13 (11%)	12 (11%)	2 (2%)
Angina pectoris	5	5	0
Arrhythmia	1	0	0
Bradycardia	0	1	0
Left ventricular dysfunction	2	0	0
Palpitations	3	2	1
Sinus tachycardia	0	1	0
Tachycardia	4	4	1
Grade 3/4 adverse events			
Febrile neutropenia	2 (2%)	2 (2%)	2 (2%)
Neutropenia	3 (3%)	5 (4%)	2 (2%)
Diarrhoea	1 (1%)	4 (4%)	1 (1%)
Stomatitis	1 (1%)	4 (4%)	3 (3%)
Infection	0	0	1 (1%)
Pneumonia	1 (1%)	0	0
Arthralgia	0	3 (3%)	3 (3%)
Myalgia	1 (1%)	1 (1%)	1 (1%)
Peripheral neuropathy	1 (1%)	2 (2%)	0
Left ventricular dysfunction	2 (2%)	0	0
LVEF worst value during treatment and follow-up			
NCI-CTC grade 0	84 (73%)	94 (83%)	83 (84%)
NCI-CTC grade 1*	26 (23%)	18 (16%)	13 (13%)
NCI-CTC grade 2†	2 (2%)	1 (1%)	1 (1%)
NCI-CTC grade 3‡	2 (2%)	0	0

Data are n (%). LVEF=left ventricular ejection fraction. NCI-CTC=National Cancer Institute common toxicity criteria. *Asymptomatic reduction of 10% or more, but less than 20% of baseline. †Asymptomatic reduction to lower limit of normal or 20% or more of baseline. ‡Congestive heart failure, responsive to treatment.

Table 3: **Selected adverse events and LVEF in the safety population**

Table 1 summarises baseline characteristics. As expected, women in the HER2-negative group were less likely to have inflammatory or hormone receptor-negative disease than were those in the HER2-positive groups. They were also slightly younger than were those with HER2-positive cancer (table 1).

215 (91%) patients with HER2-positive disease completed the planned ten cycles of chemotherapy, although 42 (18%) needed dose reductions. Trastuzumab was stopped before 1 year of treatment was completed in eight (7%) patients. Breast and axillary radiotherapy and adjuvant hormonal treatment were evenly distributed across treatment groups. 19 (16%) patients with HER2-positive disease assigned to chemotherapy alone crossed over to receive adjuvant trastuzumab.

After a median follow-up of 3·2 years, 87 primary outcome events had been reported in the HER2-positive groups (35 in the HER2-negative group). 3-year event-free survival was 71% (95% CI 61–78) in the trastuzumab group and 56% (46–65) in the non-trastuzumab group. The unadjusted HR for risk of a primary outcome event in the trastuzumab group compared with the HER2-positive chemotherapy alone group was 0·59 (95% CI 0·38–0·90; p=0·013) (figure 2A), corresponding to a 41% reduction in risk of recurrence, progression, or death with addition of trastuzumab. Benefits of trastuzumab were seen in all subgroups tested, including patients with inflammatory disease (figure 3). Regression analysis of stratification variables confirmed that treatment with trastuzumab was the only variable to significantly affect event-free survival (adjusted HR 0·58, p=0·0126) (figure 2A).

For HER2-positive patients, the number of deaths did not differ significantly between the trastuzumab group and the chemotherapy alone group at time of reporting (figure 2B). 3-year overall survival was 87% (95% CI 79–92) and 79% (70–86), respectively. Local, regional, and distant recurrences were all less frequent for trastuzumab-treated patients than for those with HER2-positive cancer treated with chemotherapy alone. Event-free survival of patients with HER2-positive disease who were not treated with trastuzumab did not differ from that of those with HER2-negative cancer receiving the same regimen (figure 2C). Event-free survival in the group with HER2-negative tumours at

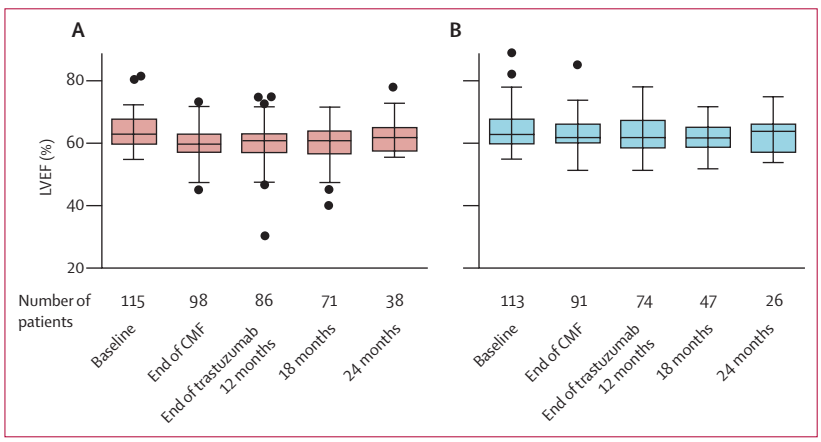


Figure 4: **Left ventricular ejection fraction for women with HER2-positive tumours receiving chemotherapy and trastuzumab (A) or chemotherapy alone (B)**
Central horizontal lines show medians, limits of shaded boxes show 50th percentiles, horizontal lines outside boxes show 90th percentiles, and dots show outliers (outside 90th percentiles). LVEF=left ventricular ejection fraction. CMF=cyclophosphamide, methotrexate, and fluorouracil.

3·2 years was 67% (56–75) and overall survival was 86% (77–92).

Trastuzumab significantly improved rates of pathological complete response in patients with HER2-positive disease (table 2). Response rates did not differ in patients with HER2-positive disease who were not treated with trastuzumab compared with those with HER2-negative disease (table 2).

Adverse events were much the same in the three groups, with no increase in grade 3 and 4 non-cardiac toxic effects in the trastuzumab group (table 3). Although fewer patients in the trastuzumab group maintained normal left ventricular ejection fraction throughout the study, most reductions were grade 1 in severity. During treatment and follow-up only two patients had a grade 2 decrease (asymptomatic) and two (1·7%; 95% CI 0·5–6·0) a reversible grade 3 decrease (congestive heart failure, classified as NYHA class III) (table 3, figure 4).

Discussion

The results of the NOAH study have shown that in patients with HER2-positive locally advanced or inflammatory breast cancer, addition of 1 year of trastuzumab (starting as neoadjuvant and continuing as adjuvant therapy) to neoadjuvant chemotherapy improved overall response rates, almost doubled rates of pathological complete response, and reduced risk of relapse, progression, or death compared with patients who did not receive trastuzumab. We recorded a benefit of trastuzumab in all subgroups tested, including women with inflammatory disease (27% of HER2-positive patients) who benefited substantially from trastuzumab.

Our results consolidate those of other studies of trastuzumab in the neoadjuvant setting. In these mainly non-randomised studies, pathological complete response rates (variously defined) ranged from 17% to 73%, and were better than they were in historical[6] or concurrent HER2-negative controls.[24,25] One randomised trial in patients with operable non-inflammatory disease was stopped early when the pathological complete response rate in the trastuzumab group was more than twice as high as that of the control group (65% *vs* 26%).[26] Patient numbers in this study were small, but preliminary results from another randomised study also show a doubling in pathological complete response rate in the trastuzumab group.[27] These response rates to primary systemic therapy are a surrogate for relapse-free[28] and overall survival in patients who were unselected for HER2 status.[29] Results of our trial show an improvement in event-free survival and pathological complete response rate in patients with HER2-positive disease. Pathological complete response rate could be regarded as a possible primary endpoint and early indicator of benefit in neoadjuvant studies of HER2-targeted agents.

We included a parallel cohort of patients with HER2-negative disease who were treated with the same chemotherapy regimen and selected with the same eligibility criteria as were those with HER2-positive disease. The criteria for HER2-negativity meant that an intermediate group of HER2-negative patients (with fluorescent in-situ hybridisation-negative disease and 2+ overexpression) was not enrolled, increasing the contrast between the HER2-negative and HER2-positive groups. HER2-positive disease has been reported to be more sensitive to neoadjuvant doxorubicin and paclitaxel than is HER2-negative disease,[30] but we did not record such different sensitivity in the NOAH trial.

Trials in the adjuvant setting have shown a survival benefit with the addition of 1 year of trastuzumab to chemotherapy.[11–13] Results showing improved survival in the trastuzumab group were not significant in our trial, and extended follow-up and an increased number of events are needed to confirm this finding. However, crossover to adjuvant trastuzumab in 17% of patients and use of trastuzumab at relapse could prevent a survival advantage being shown, despite passage of time.

Importantly, we did not compare a neoadjuvant plus adjuvant approach with adjuvant treatment alone. Therefore, we cannot conclude that the neoadjuvant component of trastuzumab treatment led to the improvement in event-free survival—the same improvement might have been seen with 1 year of adjuvant trastuzumab alone. Nevertheless, the encouraging improvements in pathological complete response rate seen when neoadjuvant trastuzumab was given in combination with neoadjuvant chemotherapy suggest that this approach has other advantages. For example, in patients with operable breast cancer, this treatment could improve rates of breast-conserving therapy.

Despite concurrent use of doxorubicin, paclitaxel, and trastuzumab in the NOAH trial, incidence of symptomatic cardiac failure was low (<2%) and less than was expected

(2·8–4·1%) on the basis of adjuvant trials in which trastuzumab was given concurrently with paclitaxel after completion of doxorubicin[31,32] and when trastuzumab was given as monotherapy after completion of a range of cytotoxic regimens (2%).[11] These findings support the accumulating evidence that trastuzumab can be given concurrently with anthracyclines with a low frequency of symptomatic cardiac dysfunction, provided that low cumulative doses or less cardiotoxic anthracyclines are used, and careful cardiac monitoring is done.

Although locally advanced breast cancer is relatively infrequent in affluent countries compared with non-affluent countries, it is still an area of medical need, especially in regions of the world where diagnosis tends to occur late for cultural or economic reasons. Our results suggest that neoadjuvant trastuzumab should be offered to patients with HER2-positive locally advanced or inflammatory breast cancer alongside neoadjuvant chemotherapy, in addition to the established use of adjuvant trastuzumab postsurgery.

Contributors

LG, WE, VS, AM, AL, ST, MZ, FV, MB, ML, MAC, EC, BO, MM, AB, and JB recruited and managed patients in the study and were involved in data collection. LG, PV, JB, CB, and AF participated in protocol development. PV and RB analysed the data and LG, PV, RB, and JB participated in data interpretation. LG, PV, CB, and AF prepared the report. All authors were given the opportunity to comment on the draft report and saw and approved the final version.

Conflicts of interest

LG has served on scientific advisory boards for Roche, Genentech, GlaxoSmithKline, Wyeth, Novartis, Millennium, BiogenIdec, and Eisai. JB has had consultant or advisory roles for Exelixis, Merck, Novartis, and Roche, and has received research funding from GlaxoSmithKline. AF is employed by Roche. CB has been employed by Roche, has held consultancies for ONO Pharma, Cellact, Acacia, Michelangelo, BTG Ltd, Kuros Biosurgery, Micromet AG, Bioenvision, Norgine, and Piramed, and has held stock in GlaxoSmithKline. WE, VS, AM, AL, ST, MZ, FV, MB, ML, MAC, EC, BO, MM, AB, RB, and PV declare that they have no conflicts of interest.

Acknowledgments

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Active NOAH participating centres

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